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Key Features

- › Cutaneous unmyelinated, polymodal sensory C-fibers have afferent functions to mediate cold, warmth, touch, pain, and itch to the CNS.
- › Polymodal sensory C-fibers mediate also efferent functions by the release of neuropeptides.
- › CGRP released from sensory nerves has an impact on keratinocyte differentiation, cytokine expression, and apoptosis.
- › SP from sensory fibers trigger skin mast cell degranulation upon acute immobilization stress in animals.
- › Histamine released from mast cells may act on keratinocytes to enhance production and release of nerve growth factor.
- › NGF sensitizes different neuroreceptors, including transient receptor potential V1 (TrpV1).
- › Cannabinoid agonist exhibit peripheral antinociceptive effects possibly by stimulation of β -endorphin release from keratinocytes.

Synonyms Box: Itch, pruritus

Abbreviations: *ADA* Atopic dermatitis, *CB* Cannabinoid receptor, *CGRP* Calcitonin gene-related peptide, *CNS* Central nervous system, *DRG* Dorsal root ganglia, *GDNF* Glial cell line-derived neurotrophic factor, *ETA* Endothelin receptor A, *ETB* Endothelin receptor B, *LC* Langerhans cells, *Mrgprs* Mas-related G-protein coupled receptors, *NGF* Nerve growth factor, *PAR-2* Proteinase-activated receptor-2, *PEA* Palmitoylethanolamine, *PKR* Prokineticin receptor,

SP Substance P, *THC* Tetrahydrocannabinol, *TrkA* Tyrosine kinase A, *Trp* Transient receptor potential, *VIP* Vasoactive intestinal peptide

2.1 Introduction

Acting as border to the environment, the skin reacts to external stimuli such as cold, warmth, touch, destruction (pain), and tickling [e.g., by parasites (itch)]. The modality-specific communication is transmitted to the

central nervous system (CNS) by specialized nerve fibers and sensory receptors. In the skin, dermal myelinated nerve fibers such as A β - and A δ -fibers transmit touch and other mechanical stimuli (e.g., stretching the skin) and fast-conducting pain [46]. Unmyelinated C-fibers in the papillary dermis and epidermis are specialized to stimuli such as cold, warmth, burning, or slow conducting pain and itch [41,84]. In the epidermis, two major classes of sensory nerve fibers can be distinguished (Table 2.1) by their conduction velocity, reaction to trophic stimuli (e.g., nerve growth factor, glial cell-line derived neurotrophic factor), and expression of neuropeptides and neuroreceptors [3,115,116]. This complex system enables the CNS

to clearly distinguish between incoming signals from different neurons in quality and localization. Moreover, C-fibers have contacts and maintain cross-talk with other skin cells such as keratinocytes, Langerhans cells, mast cells, and inflammatory cells. This enables sensory nerves to function not only as an afferent system that conducts stimuli from the skin to the CNS, but also as an efferent system that stimulates cutaneous cells by secreting several kinds of neuropeptides. In addition, sensory sensations can be modified in intensity and quality by this interaction (Table 2.2). In this chapter, an overview is given on the neuroreceptors and mediators of C-fibers involved in the sensory system of the skin and their communication with other skin cells.

Table 2.1 The two major epidermal C-fiber classes^a

	Peptidergic	Non-peptidergic
Conducting velocity	0.5 m s ⁻¹	1.0 m s ⁻¹
Diameter	0.3–1.0 μ m	0.3–1.0 μ m
Localization in epidermis	Up to stratum spinosum	Up to granular layer
Receptors (receptor for growth factors, other receptors)	trkA, p75, e.g. Histamine receptor, Trp-group	c-RET, binding of Isolectin B4, Mrgprd, TrpV1
Neurotransmitters	Peptidergic, e.g., SP, CGRP	Non-peptidergic
Trophic factor (both present in keratinocytes)	Nerve growth factor (NGF)	Glial cell-line derived neurotrophic factor (GDNF)
Function	Itch, cold, warmth, burning pain, noxious heat	Mechanical stimuli, warmth, pain

^a98% of all epidermal nerve fibers

Table 2.2 Function of neuroreceptors on C-fibers

Receptor	Ligand	Function
Histamine receptors: H1–H4	Histamine	Pruritus (H1 and H4 receptor), neurogenic inflammation; sensitized by bradykinin, prostaglandins
Endothelin receptors: A, B	Endothelin 1, 2, 3	ETA: Pruritus, mast cell degranulation, inflammation, increase of TNF-alpha, IL-6, VEGF, TGF-beta1 ETB: suppression of pruritus
TrpV1	Noxious heat (>42°C), protons, capsaicin, anandamide	Cold, heat, burning pain, burning pruritus, noxious heat sensitized by NGF, galanin, bradykinin
TrpV2	Noxious heat (>52°C)	Pain induced by heat
TrpV3	Warmth (>33°C)	Warmth
TrpV4	Warmth (~25°C)	Warmth
TrpM8 (on A δ -fibers)	Cold (8–28°C), menthol, icilin	Cold
TrpA1 (AnkTM1)	Noxious cold (<17°C), wasabi, horseradish, mustard	Pain induced by cold, burning

(continued)

Table 2.2 (continued)

Receptor	Ligand	Function
PAR-2	Tryptase, trypsin	Pruritus, neurogenic inflammation
Opioid receptors: Mu-, delta-receptor	Endorphins, enkephalins	Suppression of pain, pruritus, and neurogenic inflammation
Cannabinoid receptors CB1, CB2	Cannabinoids CB1: anandamide CB2: PEA	Suppression of itch, pain and neurogenic inflammation, release of opioids

2.2 Neurojunctions with Cutaneous Cells and Efferent Functions of the Skin Nervous System

Unmyelinated C-fibers are found in the papillary dermis as well as in the epidermis up to the granular layer. Electron microscopic and confocal scanning microscopy investigations demonstrated C-fibers having contacts to keratinocytes by slightly invaginating into keratinocyte cytoplasm [12,33,36]. These neuro-epidermal junctions are discussed as representing synapses [12] since the adjacent plasma membranes of keratinocytes were slightly thickened, closely resembling post-synaptic membrane specializations in nervous tissues. The nerve fibers cross-talk with the connected cells and exert, in addition to sensory function, trophic and paracrine functions. These efferent functions are mediated by neuropeptides [e.g., substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP)] released upon antidromic activation of the peripheral terminals of unmyelinated C-fibers [77]. For example, nerve fibers were reported to influence epidermal growth and keratinocyte proliferation [38]. CGRP released from sensory nerves was demonstrated to have an impact on keratinocyte differentiation, cytokine expression, and apoptosis through intracellular nitric oxide (NO) modulation and stimulation of nitric oxide synthase (NOS) activity [24]. This connection also has an influence on several diseases; for example, wound healing is disturbed in diabetic patients due to small fiber neuropathy and decreased release of SP from nerve fibers [32].

Neuronal connections to Langerhans cells [31,37], melanocytes [34], and Merkel cells [58] have also been demonstrated. It was observed that CGRP-containing C-nerve fibers were associated with epidermal Langerhans cells (LC), and CGRP was found to be present at the surface of some cells. Further, CGRP

was shown to inhibit LC antigen presentation [37]. In a confocal microscopic analysis, intraepidermal nerve ending contacts with melanocytes were found [34]. Thickening of apposing plasma membranes between melanocytes and nerve fibers, similar to contacts observed in keratinocytes, were confirmed. Stimulation of cultured human melanocytes with CGRP, SP, or vasoactive intestinal peptide (VIP) led to increased DNA synthesis rate of melanocytes by the cAMP pathway in a concentration- and time-dependent manner mediated [34].

In the papillary dermis, direct connections between unmyelinated nerve fibers and mast cells were found [53,109]. It is debated whether this connection has relevance in healthy human skin [105]. However, experimental studies showed that intradermally injected SP induces release of histamine via binding to NKR on mast cells and thereby acts as a pruritogen [15]. Other investigations demonstrated SP-induced release of pruritogenic mediators from mast cells under pathologic conditions [70,99]. Furthermore, a connection between neuropeptides, mast cells, and stress could be shown in animal studies [82]. Acute immobilization stress triggered skin mast cell degranulation via SP from unmyelinated nerve fibers. Pruritus, whealing, and axon-reflex erythema due to histamine release appear in human skin after intradermal injection of VIP, neurotensin, and secretin. Also somatostatin was reported to stimulate histamine release from human skin mast cells [15].

Neuropeptides such as SP and CGRP act on blood vessels inducing dilatation and plasma extravasation, resulting in neurogenic inflammation with erythema and edema [94]. SP upregulates adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) [73], is chemotactic for neutrophils [5], and induces release of cytokines such as interleukin (IL)-2 or IL-6 from them [18]. In sum, release of neuropeptides from

nerve fibers enables dermal inflammation by acting on vessels and on inflammatory cells. Interestingly, increased SP-immunoreactive nerve fibers have been observed in certain inflammatory skin diseases such as psoriasis, atopic dermatitis, and prurigo nodularis [1,42,43].

2.3 Histamine Receptors

Histamine and the receptors H1 to H4 have been the most thoroughly studied mediator and neuroreceptors for decades. Lewis reported 70 years ago that intradermal injection of histamine provokes redness, wheal, and flare (so called triple response of neurogenic inflammation) accompanied by pruritus [52]. Accordingly, histamine is used for most experimental studies investigating neurogenic inflammation and itching [78]. Histamine is stored in mast cells and keratinocytes while H1 to H4 receptors are present on sensory nerve fibers and inflammatory cells [35,100]. Thus, histamine-induced itch may be evoked by release from mast cells or keratinocytes. Only recently it was reported that, in addition to histamine receptor 1 (H1), H3 and H4 receptors on sensory nerve fibers are also involved in pruritus induction in mice [6,96]. Interestingly, histamine released from mast cells may act on keratinocytes to enhance production and release of nerve growth factor (NGF) [47]. In turn, NGF induces histamine release from mast cells and sensitizes different neuroreceptors, including transient receptor potential V1 (TrpV1) [113]. Current studies suggest that histamine also regulates SP release via prejunctional histamine H3 receptors that are located on peripheral endings of sensory nerves [67]. This may have an impact on SP-dependent diseases such as ulcerations. Accordingly, a current study demonstrated that mast cell activation and histamine are required for normal cutaneous wound healing [106].

2.4 Endothelin Receptors

Endothelin (ET) -1, -2, and -3 produced by endothelial cells and mast cells induce neurogenic inflammation associated with burning pruritus [48,108]. Endothelin binds to two different receptors, endothelin receptor A (ETA) and ETB, which are present on mast cells [57]. Injected into the skin, ET-1 induces mast cell

degranulation and mast cell-dependent inflammation [59]. Furthermore, ET-1 induces TNF- α and IL-6 production, enhanced VEGF production, and TGF- β 1 expression by mast cells [57]. ET-1 was therefore identified to participate in pathological conditions of various disorders via its multi-functional effects on mast cells under certain conditions. For example, ET-1 contributes to ultraviolet radiation (UVR)-induced skin responses such as tanning or inflammation by involvement of mast cells [59]. Interestingly, ET-1 was also identified to display potent pruritic actions in the mouse, mediated to a substantial extent via ETA while ETB exerted an antipruritic role [101].

2.5 Trp-Family

The transient receptor potential (TRP) family of ion channels is constantly growing and to date comprises more than 30 cation channels, most of which are permeable for Ca²⁺. On the basis of sequence homology, the Trp family can be divided into seven main subfamilies: the TrpC (“Canonical”) family, the TrpV (“Vanilloid”) family, the TrpM (“Melastatin”) family, the TrpP (“Polycystin”) family, the TrpML (“Mucolipin”) family, the TrpA (“Ankyrin”) family, and the TrpN (“NOMPC”) family. Concerning a role in cutaneous nociception, the TrpV and the TrpM groups are both expressed on sensory nerve fibers with different functions [68].

2.5.1 TrpV1: The Capsaicin Receptor

The TrpV1 receptor (vanilloid receptor, VR1) is expressed on central and peripheral neurons [68]. In the skin, the TrpV1 receptor is present on sensory C- and A δ -fibers [87]. Different types of stimuli activate the receptor such as low pH (<5.9), noxious heat (>42°C), the cannabinoid/endovanilloid anandamide, leukotrien B4, and exogenous capsaicin. Trp receptors act as nonselective cation-channels, which open after stimulation and enable ions inward into the nerve fiber, resulting in a depolarization. As a result, for example, after capsaicin application, TrpV1 is stimulated to either transmit burning pain or a burning pruritus. Because of antidromic activation, C-fibers release neuropeptides, which mediate neurogenic inflammation. Upon chronic stimulation, TrpV1 receptor signaling exhibits desensitization in a

Ca²⁺-dependent manner, such as upon repeated activation by capsaicin or protons [111]. The desensitized receptor is permanently opened with a following steady-state of cations intra- and extracellular. This hinders depolarization of nerve fiber and the transmission of either itch or burning pain. Moreover, neuropeptides such as SP are depleted from the sensory nerve fibers; the axonal transport of both neuropeptides and NGF in the periphery is slowed. This mechanism is used therapeutically upon long-term administration of capsaicin for relief of both localized pain and localized pruritus. Clinically, the first days of the therapy are accompanied by burning, erythema, or flare induced by the neurogenic inflammation. After this initial phase, pain and itch sensations are depressed as was demonstrated in many studies and case reports [83]. Like the histamine receptor, the TrpV1 receptor may be sensitized by bradykinin and prostaglandins, as well as by NGF [39,81,113], with lowering of the activation threshold and facilitated induction of pain and itch. For example, instead of noxious heat, moderate warmth may activate a sensitized receptor.

The topical calcineurin inhibitors pimecrolimus and tacrolimus have been introduced during the past years as new topical anti-inflammatory therapies. The only clinically relevant side-effect is initial burning and stinging itch with consequent rapid amelioration of pruritus. This resembles neurogenic inflammation induced by activation of the TrpV1 receptor. Recent animal studies provide evidence that both calcineurin inhibitors bind to the TrpV1 [80,90]. It was demonstrated that topical application of pimecrolimus and tacrolimus is followed by an initial release of SP and CGRP from primary afferent nerve fibers in mouse skin [90]. Animal studies proved that the Ca²⁺-dependent desensitization of TrpV1 receptor might be, in part, regulated through channel dephosphorylation by calcineurin [61,111].

2.5.2 Thermoreceptors

2.5.2.1 Heat Receptors: TrpV2, TrpV3, TrpV4

Three transient receptor potential (Trp) receptors are activated by different ranges of warmth or heat. TrpV2 is activated by noxious heat above 52°C; TrpV3 mediates warm temperature above 33°C, and TrpV4 also is activated by temperature around 25°C

[13,14,50,71,98,110]. TrpV4 may also act as a cold receptor as shown by the binding of camphor, which induces a cold-feeling [71]. All three thermoreceptors are also present on keratinocytes. Recent animal studies suggest that skin surface temperature has an influence on epidermal permeability barrier. At temperatures 36–40°C, barrier recovery was accelerated. Temperatures of 34 or 42°C led to a delayed barrier recovery [19]. This suggested that TrpV is involved in epidermal barrier homeostasis. However, all of these receptors were defined quite recently and their expression patterns in the skin as well as detailed non-neuronal function await further exploration.

2.5.2.2 Cold Receptors: TrpM8, TrpA1

TrpM8 (CMR1) is a cold receptor expressed on myelinated A δ -fibers that is stimulated by 8–28°C. Also menthol and icilin activate the TrpM8 and thereby may act as a therapeutic tool in the cold-mediated suppression of itch [68]. Another cold receptor, TrpA1 (ANKTM1), has a lower activation temperature (<17°C) compared to the TrpM8 receptor and is also activated by wasabi, horseradish, mustard, bradykinine, as well as tetrahydrocannabinol (THC) [45,71,95]. TrpA1 is found in a subset of nociceptive sensory neurons where it is co-expressed with TrpV1 but not TrpM8. It was shown that lowering the skin temperature by cooling reduced the intensity of experimentally induced itch [11]. A similar effect was achieved with menthol, although the skin temperature was not decreased [11]. It was concluded that these findings suggest a central inhibitory effect of cold sensitive A δ -fiber activation on itch. A role in cold hyperalgesia in inflammatory and neuropathic pain is assumed; however, the underlying mechanisms of this enhanced sensitivity to cold are poorly understood [65]. It has been speculated that cold hyperalgesia occurs by NGF mediating an increase in TrpA1 receptors on nerve fibers.

2.6 Proteinase-Activated Receptor 2

The proteinase-activated receptor-2 (PAR-2) was demonstrated on sensory nerve fibers and is activated by mast cell mediators such as tryptase [92]. Activation leads to induction of pruritus and

neurogenic inflammation comparable to effects induced upon histamine release from mast cells [66,102]. In atopic dermatitis (AD), PAR-2 expression was enhanced on primary afferent nerve fibers in the lesional skin, suggesting that this receptor is involved in pathophysiology of pruritus in AD [93]. This may also explain the inefficacy of antihistamines in AD as they do not block the tryptase-mast cell axis. Cutaneous mast cells also express PAR-2, suggesting an additional autocrine mechanism [62]. PAR-2 was recently suggested to also be involved in pain mechanisms. Activation of PAR-2 is reported to induce sensitization of primary nociceptors along with hyperalgesia [21]. Together, these results suggest PAR-2 to be involved in cutaneous nociception mainly during inflammation.

2.7 Opioid Receptors

Two opioid receptors, the μ - and δ -receptor, have been demonstrated on sensory nerve fibers [85,86]. Opioid peptides such as β -endorphin, enkephalins, and endomorphins act on capsaicin-sensitive nerve fibers to inhibit the release of inflammatory neuropeptides such as SP, neurokinin A, and CGRP [51,74]. In previous studies, it was shown that peripheral opioid receptors mediate antinociceptive effects preferentially by activation of the μ -receptor and less by δ -receptor [91]. Application of peripheral morphine inhibited responses to both mechanical and thermal stimuli in inflamed skin, suggesting that peripheral opioids might modulate pain responses [107]. These findings suggest that peripheral opioid receptors act as inhibitory receptors in the skin.

In contrast, in the central nervous system, clinical and experimental observations suggest that pruritus can be evoked or intensified by endogenous or exogenous opioids [7,29,49,76]. For example, systemically administered morphine suppresses pain but induce pruritus [97]. This phenomenon can be explained by activation of spinal opioid receptors, mainly μ - and to a lesser extent κ - and δ -opioid receptors, on pain transmitting neurons, which induce analgesia, often combined with induction of pruritus [78]. Reversing this effect by μ -opioid antagonists results thereby in inhibition of pruritus. Accordingly, several experimental studies have demonstrated that different μ -opioid receptor antagonists may significantly diminish pruritus [8,60].

2.8 Cannabinoid Receptors

Up to now, two cannabinoid receptors, CB1 and CB2, have been defined precisely by their wide expression in the CNS and on immune cells [20,56,63]. CB1 was described as being densely localized in the CNS; recent studies revealed an additional expression of CB1 in peripheral tissue, that is, primary afferent neurons [2,16,72]. CB2 receptors were mainly found in the periphery, for example, on T-lymphocytes, mast cells [26,30], and also on rat spinal cord [112]. Both receptors were recently found to be expressed also on cutaneous sensory nerve fibers, mast cells, and keratinocytes [88].

Topical application of cannabinoid agonists leads to inhibition of pain, pruritus, and neurogenic inflammation [23,75,89]. During inflammation, CB1 expression in primary afferent neurons and transport to peripheral axons is increased and contributes thereby to enhanced antihyperalgesic efficacy of locally administered CB1 agonist [4]. In addition, it was demonstrated that injections of the CB2 agonist palmitoylethanolamine (PEA) may inhibit experimental NGF-induced thermal hyperalgesia [27].

However, the antinociceptive effects are believed to be mediated in part by opioid and vanilloid mechanisms and not directly by activation of cannabinoid receptors. For example, it was shown that the CB1 agonist anandamide binds to the TrpV1 receptor [114] and that topical cannabinoids directly inhibit TrpV1 functional activities via a calcineurin pathway [69]. Moreover, it was demonstrated that the antinociceptive effects of CB2 agonists can be prevented by the μ -opioid receptor-antagonist naloxone [28,104]. Interestingly, the cannabinoid agonist AM1241 stimulates β -endorphin release from rat skin tissue and from cultured human keratinocytes [40]. In sum, cannabinoid receptors seem to exert a central role in cutaneous nociception mediating direct and indirect effects and therefore represent interesting targets for the development of antinociceptive therapies.

2.9 Trophic Factors

2.9.1 Nerve Growth Factor

Neurotrophins have been found in recent years to play a major role in skin homeostasis and inflammatory diseases. One member of this family, NGF, has several

regulatory functions in cutaneous nociception, cutaneous nerve development, and reconstruction after injury through action on peptidergic C-fibers [9,64]. In epidermal keratinocytes, NGF production underlies neuropeptide release. After release of neuropeptides by a nociceptive stimulus, an upregulation of the expression of NGF and NGF secretion from the keratinocytes is induced [17]. Released NGF acts on skin nerves to sensitize neuroreceptors towards noxious thermal, mechanical, and chemical stimuli (see above) and is transported along the axon towards the dorsal root ganglia (DRG) to induce upregulation of a variety of proteins involved in neuronal growth and sensitivity. These mechanisms lead to altered peripheral nociception, for example, facilitated induction of pruritus and pain. For example, prolonged treatment of rats with moderate doses of NGF is sufficient to stimulate neuropeptide synthesis in primary afferent neurons without causing long-lasting changes in thermal nociceptive threshold [79]. Moreover, application of NGF also enhances capsaicin-evoked thermal hyperalgesia [10]. In cutaneous inflammatory diseases, NGF was demonstrated to be over-expressed in prurigo nodularis, and in AD where it is speculated to contribute to the neurohyperplasia of the disease [22,44], as well as in allergic diseases [64].

2.9.2 Glial Cell Line-Derived Neurotrophic Factor (GDNF)

During embryonic development, nociceptors are dependent on NGF, but a large subpopulation lose this dependence during embryonic and postnatal life and become responsive to the transforming growth factor beta family member, glial cell line-derived growth factor (GDNF). The family comprises members such as artemin, neurturin and glial cell line-derived growth factor, which are involved in the induction and maintenance of pain and hyperalgesia [3]. These factors act on non-peptidergic C-fibers [115,116] and expression of GDNF in the skin can change mechanical sensitivity [3]. More importantly, GDNF sensitizes thermal nociceptors towards cold or heat hyperalgesia by potentiation of TrpV1 signaling or increased expression of TrpA1 [25,54,55]. In the DRG, exposure to GDNF, neurturin, or artemin potentiate TrpV1 function at doses 10–100 times lower than NGF. Moreover, GDNF family members induced capsaicin responses in a subset of neurons that were previously insensitive to capsaicin [55].

Exposure of nerve fibers to GDNF induces, in addition, expression of prokineticin receptors (PKR) in the nonpeptidergic population of neurons. These receptors cause heat hyperalgesia by sensitizing TRPV1 [103].

Summary for the Clinician

The skin is equipped with a dense network of specialized nerve fibers for the sensation of external stimuli such as cold, warmth, touch, pain, and itch. During the past years, many neuroreceptors were identified on sensory nerve fibers, which mediate these sensations and respond to external stimuli. The chronification of sensations such as pain and itch underlie complex mechanisms such as sensitization of neuroreceptors. Several modern therapies are yet identified to interact with these mechanism and to achieve the clinical relief of peripheral pain and pruritus.

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